From Fluorescence Probe to NIRI/T_1 –T_2 Dual-Mode MRI Multimodal Nanoprobe for Alzheimer's Disease

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The lack of amyloid (Aβ)-targetability and poor blood-brain barrier (BBB) penetrability of existing contrast agents would not allow to visualize Aβ plaques by means of magnetic resonance imaging (MRI) for diagnosis and prognosis of Alzheimer's disease (AD). We present herein an advanced multimodal theranostic nanoprobe that can bind Aβ aggregates, conduct NIR fluorescence imaging, and perform dual-mode T_1- and T_2-weighted MR imaging as well as inhibit Aβ self-aggregation and exhibit neuroprotection against Aβ-induced toxicity for *in vivo* real-time detection and visualization of Aβ plaques for precise early diagnosis of AD. The nanoprobe was designed and developed from silica-enclosed superparamagnetic iron oxide nanoparticles that were surface-functionalized by cyanine fluorophore conjugated gadolinium(III) complex molecular dyads. This versatile nanoprobe showing excellent biocompatibility, Aβ targetability as well as BBB permeability was highly effective and sensitive for *in vivo* and *ex vivo* NIR fluorescence imaging of Aβ aggregates in various age groups of APP/PS1 double transgenic (Tg) AD mouse model, Furthermore, the greatly enhanced longitudinal relaxivity (r_1 = 43.68 mM^{-1} s^{-1}) and large transverse relaxivity (r_2 = 110.89 mM^{-1} s^{-1}) enabled the nanoprobe for highly sensitive real time *in vivo* and *ex vivo* dual-mode T_1- and T_2-weighted MR imaging of Aβ aggregates in various age groups of AD mice enabling the differentiation from the normal counterparts. This work marked the first successful development of Aβ-specific NIRI/dual-mode T1- and T2-weighted MRI multimodal theranostic nanoprobe for visualization of Aβ aggregates *in vivo* by using complementary modalities for improved diagnosis of AD. In addition, its capabilities of inhibiting Aβ aggregation and protecting against Aβ-induced toxicity made it highly versatile for practical applications.